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Hulka, Lea M ; Wagner, Michael ; Preller, Katrin H ; Jenni, Daniela ; Quednow, Boris B

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# Blue–yellow colour vision impairment and cognitive deficits in occasional and dependent stimulant users

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## Abstract

Specific blue–yellow colour vision impairment has been reported in dependent cocaine users and it was postulated that drug-induced changes in retinal dopamine neurotransmission are responsible. However, it is unclear whether these changes are confined to chronic cocaine users, whether they are specific for dopaminergic stimulants such as cocaine and amphetamine and whether they are related to cognitive functions such as working memory, encoding and consolidation. In 47 occasional and 29 dependent cocaine users, 23 MDMA (commonly known as ‘ecstasy’) users and 47 stimulant-naïve controls, colour vision discrimination was measured with the Lanthony Desaturated Panel D-15 Test and memory performance with the Auditory Verbal Learning Test. Both occasional and dependent cocaine users showed higher colour confusion indices than controls. Users of the serotonergic stimulant MDMA (26%), occasional (30%) and dependent cocaine users (34%) exhibited more frequent blue–yellow colour vision disorders compared to controls (9%). Inferior performance of MDMA users was caused by a subgroup with high amphetamine co-use (55%), while MDMA use alone was not associated with decreased blue–yellow discrimination (0%). Cognitive performance was worse in cocaine users with colour vision disorder compared to users and controls with intact colour vision and both colour vision impairment and cognitive deficits were related to cocaine use. Occasional cocaine and amphetamine use might induce blue–yellow colour vision impairment, whereas the serotonergic stimulant MDMA does not impair colour vision. The association between colour vision impairment and cognitive deficits in cocaine users may reflect that retinal and cerebral dopamine alterations are linked to a certain degree.

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**Key words:** Chromatic vision, recreational cocaine use, cognition, memory, lanthony D-15.

## Introduction

The psychostimulant cocaine exerts its reinforcing effect primarily via inhibiting the uptake of dopamine in the nucleus accumbens and additional structures of the reward system (Ritz *et al.* 1987). Numerous imaging studies with dependent cocaine users have provided evidence for blunted dopamine neurotransmission (Martinez *et al.* 2004, 2007, 2009, 2011; Volkow *et al.* 1993, 1997; Wu *et al.* 1997) and abnormalities in cerebral glucose metabolism in the

prefrontal cortex (PFC) and further limbic areas (Bolla *et al.* 2004; Volkow *et al.* 1992), leading to widespread motivational, cognitive, behavioural and psychiatric consequences (Bolla *et al.* 2004). The central dopamine system holds a pivotal role in the mediation of PFC function (Braskie *et al.* 2008; Nieoullon, 2002; Vernaleken *et al.* 2007), which is crucial for attention, working memory and executive functions (Benton, 1994). Additionally, it was recently demonstrated that dopamine neurotransmission is critically involved in encoding, consolidation and retrieval of declarative memory (Breitenstein *et al.* 2006a,b; Morris *et al.* 2003; Whiting *et al.* 2007, 2008). Consequently, neuropsychological impairment has been consistently reported for cocaine-dependent subjects across several areas of cognitive functioning, including attention and

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executive function, verbal learning and memory (Fernandez-Serrano *et al.* 2009; Goldstein *et al.* 2004; Kelley *et al.* 2005; Woicik *et al.* 2009).

Dopamine also exists in high concentrations in the retina, where it is localized in the amacrine and interplexiform retinal cells (Bodis-Wollner & Tzelepi, 1998; Dowling, 1990; Witkovsky, 2004). Dopamine acts in a complex fashion on visual information processing and is involved in the regulation of lateral inhibition, centre-surround antagonism and light adaptation, promoting the light-driven cone input and reducing the rod input (Brandies & Yehuda, 2008; Sannita, 1995; Witkovsky, 2004). Moreover, dopamine may also be involved in chromatic processing by modulating horizontal cell functioning and the cone-horizontal cell connectivity (Ahnelt & Kolb, 1994; Djamgoz *et al.* 1997). Indeed, abnormal colour discrimination has been reported for several neuropsychiatric conditions featuring altered dopaminergic mechanisms, such as Parkinson's and Huntington's disease, Tourette syndrome and attention deficit hyperactivity disorder (Djamgoz *et al.* 1997; Melun *et al.* 2001; Paulus *et al.* 1993; Pieri *et al.* 2000; Sartucci *et al.* 2003; Tannock *et al.* 2006). These conditions were mainly associated with specific colour vision impairment (CVI) along the tritan (blue-hue) axis, which is usually not affected in congenital CVI. Chronic cocaine use has also been associated with blue-yellow CVI. Desai *et al.* (1997) reported that >48% of dependent cocaine-withdrawn patients exhibited CVI along the tritan axis in comparison to 6.5% of the control subjects. Furthermore, significantly decreased blue cone b-wave electroretinogram (ERG) amplitudes were discovered in recently withdrawn cocaine-dependent patients and lower blue cone b-waves were associated with stronger cocaine craving in these patients (Roy *et al.* 1996, 1997a). A subsequent longitudinal investigation revealed that the CVI persisted together with cocaine craving over at least 8 wk (Roy *et al.* 1997b). The latest study of Roy *et al.* (2003) showed that patients with a reduced blue cone b-wave amplitude exhibited significantly lower concentrations of the major dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF). The authors concluded that blue-yellow CVI in cocaine-dependent subjects reflects a central hypodopaminergic state, as was previously demonstrated in several molecular imaging studies (Martinez *et al.* 2007; Volkow *et al.* 1990, 1997). However, it has not been investigated so far if CVI in cocaine users is correlated with behavioural or cognitive deficits, which could further indicate a potential association with frontostriatal dopamine dysfunction (Backman & Farde, 2001). Prior studies primarily

focused on chronic/dependent cocaine users and it remains unclear if occasional cocaine users show CVI. Neither has it been examined if other stimulant drugs with different mechanisms of action, such as MDMA (commonly known as 'ecstasy'), also induce CVI. The substituted amphetamine derivative MDMA mainly acts on the serotonin system and may ultimately induce serotonergic terminal loss but has not been shown to cause long-term alterations of the dopamine system (Capela *et al.* 2009; Green *et al.* 2003).

In the present study, we aimed to clarify at which degree of cocaine exposure CVI occurs and how specific it is for cocaine use. Moreover, we investigated the potential association between CVI and cognitive alterations in stimulant users. (1) We hypothesized that colour vision, and in particular blue-yellow colour vision, is specifically impaired by the use of stimulants altering the dopamine system (cocaine and amphetamine) and not by substances mainly targeting other neurotransmitter systems such as the serotonin releaser MDMA. (2) We expected that cocaine-related CVI would be influenced by different patterns of cocaine use; therefore, we compared occasional, non-dependent cocaine users who had used cocaine over shorter time periods, less frequently and in smaller doses to dependent cocaine users. (3) We reasoned that cocaine users with CVI would also exhibit more pronounced cognitive deficits reflecting alterations of the central dopamine system.

## Materials and method

### Study design and subjects

The sample consisted of 48 occasional cocaine users, 30 dependent cocaine users, 24 MDMA users and 48 psychostimulant-naïve control subjects (total  $n=150$ ). Subjects were recruited in Zurich by advertisements in widely read local newspapers, different drug prevention and treatment centres, psychiatric hospitals, Internet platforms and word-of-mouth communication. Inclusion criteria were non-dependent cocaine use (1–5 g per month, DSM-IV criteria of cocaine dependence not met), dependent cocaine use ( $\geq 5$  g per month, dependence according to DSM-IV criteria) or recreational MDMA use ( $> 50$  pills/lifetime). Abstinence duration of cocaine/MDMA use had to be  $< 6$  months. Participants' age had to be between 18 and 65 yr. Exclusion criteria were Axis I or II DSM-IV psychiatric disorders other than cocaine and alcohol abuse/dependence, neurological disorders or head injury, use of opioids or prescription drugs affecting the central nervous system. Participants had to abstain from illegal substances for a minimum of 3 d and from

alcohol for at least 24 h. Urine samples were collected to ensure abstinence, whereby six occasional and 13 dependent cocaine users tested positive for cocaine. In order to take effects of acute cocaine use on colour vision into account, additional analyses were carried out to determine whether subjects with positive and negative urine toxicology differed in their colour vision performance. Several subjects of the control group had used cannabis. It was decided not to exclude them from the analyses as cocaine and MDMA users had used cannabis as well. Four subjects (one from each group) were excluded due to congenital CVI in the red-green spectrum. The study was approved by the Cantonal Ethics Committee of Zurich.

### Procedure

Neuropsychological and colour vision assessment was carried out after written informed consent was provided by all participants. Moreover, a Structured Clinical Interview for DSM-IV Disorders was carried out by a trained psychologist. To estimate pre-morbid verbal intelligence the Mehrfachwahl-Wortschatz-Intelligenztest (Lehrl, 1999) was applied. Drug use was assessed by means of the Interview for Psychotropic Drug Consumption, which has been described in detail in our previous work (Quednow *et al.* 2004). The brief version of the Cocaine Craving Questionnaire (CCQ) was used to assess current cocaine craving (Sussner *et al.* 2006; Tiffany *et al.* 1993).

### Colour vision assessment and scoring

To assess acquired CVI, the Lanthony Desaturated Panel D-15 Test (LD-15) was used (Lanthony, 1978). The test consists of a fixed reference cap and 15 movable colour caps that have to be arranged in consecutive order. Colours are of low saturation (decreased chroma) and increased lightness. The test was performed under a daylight fluorescent lamp (GTI norm daylight, D65, 6500K), providing an illumination of 1400 lux. Although no time limit was imposed for test completion, all participants completed the LD-15 within a range of 20 and 560 s (mean = 102.50, s.d.  $\pm$  72.38). Qualitative scoring is achieved by graphically scoring the test on a template that describes a hue circle based on the placement of the caps in the International Commission on Illumination colour space (Wyszecki & Stiles, 1982). Single cap inversions (e.g. 1-3-2-4- ...) are classified as minor errors, whereas cap reversals spanning two or more positions are considered major errors. For each individual, different colour vision error-type patterns [protan (red), deutan (green) and tritan/tetartan (blue-yellow) colour vision deficits]

can be derived by drawing lines between consecutive caps. Types of acquired dyschromatopsia relied on Verriest's classification: type I reflects CVI along the red-green axis; type II is a combined impairment of the red-green and blue-yellow axis; type III reflects blue-yellow axis impairment; type IV is diagnosed when no clear pattern can be determined. Quantitative scoring is based on the colour scoring method proposed by Geller (2001), who provided a table that yields the total colour distance score (TCDS) in the CIELAB space. A perfect TCDS score of 56.41 results when all the caps are arranged in consecutive order. A colour confusion index (CCI) error score can be calculated by dividing an individual's actual TCDS score by the ideal score. A CCI value of 1 constitutes the perfect score while higher values indicate CVI.

### Cognitive assessment

Verbal learning, declarative memory and executive memory functions were assessed by using a German version (Helmstaedter *et al.* 2001) of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964). The RAVLT was chosen because both cocaine and MDMA users have been shown to exhibit marked deficits in verbal learning and declarative memory (Kalechstein *et al.* 2007; Kelley *et al.* 2005). The test has been described in detail elsewhere (Quednow *et al.* 2006). In brief, the RAVLT consists of word list A containing 15 nouns (learning list), a second list B with 15 different nouns (interference list) and a third list C comprising 50 nouns including all words of lists A and B as well as 20 new words that are semantically and phonetically related (recognition list). As dependent variables were assessed: working memory span (supraspan, trial 1), encoding (learning performance,  $\Sigma$  trials 1-5), recall consistency in percentage (according to Delis *et al.* 1987), recall of interference material (list B), recall after interference (trial 6), long-term memory (delayed recall, trial 7 after 30 min), consolidation/retrieval (trial 5 minus 7) and adjusted recognition performance [ $p(A)$ ,  $p(B)$ ; Forrester & Geffen, 1991].

### Statistical analysis

Statistical analyses were performed with PASW 18.0 (SPSS Inc., USA). Qualitative data were analysed by means of frequency analyses (Pearson's  $\chi^2$  test and Fisher's exact test where appropriate) and quantitative data by analyses of variance. For *post-hoc* analyses, Sidak corrections were applied. As the assumptions of homoscedasticity and parametric distribution were not met by the variables age, years of education, drug use parameters and colour discrimination data, these

variables were log-transformed (log 10) and the constant 1 was added because the data contained 0 values. Log-transformed values are not reported. Because age, sex and alcohol/nicotine consumption were shown to have an impact on colour vision (Erb *et al.* 1999; Jackson & Owsley, 2003; Mergler *et al.* 1988; Rodriguez-Carmona *et al.* 2008), and years of education differed between groups, these parameters were introduced as covariates in analyses of covariance (ANCOVA) of the CCI. Age and years of education were introduced as covariates in ANCOVAs of memory performance. Correlation analyses (Pearson's product-moment) and binary logistic regression analyses were conducted to relate drug use parameters to deficits in colour discrimination and cognitive performance. Sensitivity and specificity of the LD-15 were calculated according to Cooper *et al.* (1979) and ICCVAM (1997). Effect sizes were calculated with G\*Power 3.1 (Faul *et al.* 2007).

## Results

### Demographic variables and drug use

Information regarding demography and verbal IQ are displayed in Table 1. Groups did not differ in sex distribution, verbal IQ and smoking status, whereas there were significant differences in age and years of education. Dependent cocaine users were significantly older ( $p < 0.001$ ) and had fewer years of education ( $p < 0.01$ – $0.001$ ) than participants from all other groups. However, MDMA users, occasional cocaine users and controls were well matched among all variables. Age and years of education were still introduced as covariates in all analyses.

The drug use pattern of all groups is shown in Table 2. Dependent cocaine users smoked significantly more cigarettes per week than controls ( $F_{3,142} = 4.24$ ,  $p < 0.01$ ; *post-hoc*  $p < 0.01$ ) and both occasional and dependent cocaine users consumed more alcohol (g/wk) than MDMA users ( $F_{3,142} = 4.031$ ,  $p < 0.01$ ; *post-hoc*  $p < 0.01$ ,  $p < 0.05$ ) but not in comparison to controls.

### Qualitative analyses of the LD-15

Qualitative analyses revealed a significant group effect regarding the presence of blue–yellow and total CVI impairment (Table 1, Fig. 1). CVI was more frequent in both, occasional [ $\chi^2_1 = 9.73$ ,  $p < 0.01$ , odds ratio (OR) 5.21] and dependent cocaine users ( $\chi^2_1 = 13.55$ ,  $p < 0.001$ , OR = 7.84), but not in MDMA users (Fisher's exact  $p = 0.159$ ), when compared to control subjects (Fig. 1). Occasional and dependent cocaine users did

not differ from each other. The most frequent type of CVI was along the blue–yellow axis (type III disorder), where occasional ( $\chi^2_1 = 6.87$ ,  $p < 0.01$ , OR 4.56) and dependent cocaine users ( $\chi^2_1 = 8.05$ ,  $p < 0.01$ , OR 5.66) showed significantly more frequent blue–yellow CVI than controls (Fig. 1). A tendency that MDMA users exhibited type III disorder more frequently than controls was found (Fisher's exact  $p = 0.07$ ). Once again, occasional and dependent cocaine users did not significantly differ from one another in the frequency of type III disorders. Although there was no statistically significant difference between the groups regarding the frequency of type II disorders, occasional and dependent cocaine users showed more frequent red–green CVI than controls and MDMA users.

Approximately half of the subjects in the MDMA group indicated that they also used amphetamine on a regular basis. Interestingly, when the MDMA group was divided into a 'low' (<150 g amphetamine lifetime, mean  $\pm$  s.d. =  $52.8 \pm 48.6$  g,  $n = 12$ ) and 'high' amphetamine user group (>150 g lifetime, mean  $\pm$  s.d. =  $371 \pm 307$  g,  $n = 11$ ), none of the low amphetamine MDMA users suffered from blue–yellow CVI, whereas in the high amphetamine MDMA group 55% showed blue–yellow CVI (Fisher's exact  $p < 0.05$ ,  $\Phi = -0.429$ ).

### Quantitative analyses

Quantitative analyses showed that the CCI differed significantly between groups (Table 1), even after controlling for age, sex, alcohol consumption, smoking and years of education ( $F_{3,137} = 3.72$ ,  $p < 0.05$ ,  $\eta^2 = 0.08$ ). *Post-hoc* analyses indicated that the CCI of occasional ( $p < 0.05$ ,  $d = 0.60$ ) and dependent cocaine users ( $p < 0.05$ ,  $d = 0.73$ ) was significantly higher than the CCI of controls. In addition, dependent cocaine users also showed significantly higher CCI scores in comparison to MDMA users ( $p < 0.05$ ). Occasional and dependent cocaine users did not differ from one another. None of the covariates were significantly related to the CCI.

Confirming the results obtained in the qualitative analysis, high amphetamine MDMA users (CCI  $1.25 \pm 0.17$ ) showed significantly inferior colour discrimination performance compared to low amphetamine MDMA users (CCI  $1.07 \pm 0.08$ ; *post-hoc*  $p < 0.01$ ;  $d = 1.21$ ) and controls (CCI  $1.09 \pm 0.14$ ,  $p < 0.01$ ;  $d = 1.10$ ), while low amphetamine users and controls did not differ (overall all groups,  $F_{2,67} = 6.91$ ,  $p < 0.01$ ,  $\eta^2 = 0.17$ ).

To investigate the impact of cannabis use across all four groups, an ANCOVA (covariates see above) with cannabis use (yes/no) and group as fixed-factors



**Table 1.** Demographic data and colour vision impairment types, CCI and TCDS

	Stimulant-naive controls ( <i>n</i> = 47)	Occasional MDMA users ( <i>n</i> = 23)	Occasional cocaine users ( <i>n</i> = 47)	Dependent cocaine users ( <i>n</i> = 29)	<i>F</i> / $\chi^2$ / <i>t</i>	df/df <sub>err.</sub>	<i>p</i>	Effect size
Age	26.85 (6.95)	23.22 (5.37)	27.21 (7.14)	35.90 (10.86)	13.47 <sup>a</sup>	3/142	<0.001	0.22 <sup>e</sup>
Sex (m/f)	39/8 (83 %, 17 %)	22/1 (96 %, 4 %)	39/8 (83 %, 17 %)	22/7 (76 %, 24 %)	3.81 <sup>b</sup>	3	0.29	
Years of education	11.55 (1.46)	11.26 (1.74)	10.96 (1.68)	9.50 (1.15)	11.45 <sup>a</sup>	3/142	<0.001	0.20 <sup>e</sup>
Verbal IQ (MWT-B)	107.06 (10.35)	101.43 (11.02)	104.11 (11.14)	103.10 (11.82)	1.62 <sup>a</sup>	3/142	0.19	
Smokers/non-smokers	35/12 (75 %, 25 %)	19/4 (83 %, 17 %)	40/7 (85 %, 15 %)	27/2 (93 %, 7 %)	4.47 <sup>b</sup>	3	0.20	
Cocaine craving (CCQ)	–	–	18.64 (9.29)	19.52 (9.12)	–0.39 <sup>d</sup>	69	0.70	
Colour vision impairment								
Type I	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1.00 <sup>c</sup>	3	1.000	
Type II	1 (2 %)	0 (0 %)	4 (9 %)	3 (10 %)	4.51 <sup>c</sup>	3	0.211	0.18 <sup>f</sup>
Type III	4 (9 %)	6 (26 %)	14 (30 %)	10 (35 %)	8.99 <sup>c</sup>	3	<b>0.029</b>	0.25 <sup>f</sup>
Type IV	0 (0 %)	0 (0 %)	0 (0 %)	1 (3 %)	4.06 <sup>c</sup>	3	0.255	0.17 <sup>f</sup>
Total	5 (11 %)	6 (26 %)	18 (38 %)	14 (48 %)	14.85 <sup>c</sup>	3	<b>0.002</b>	0.32 <sup>f</sup>
CCI	1.09 (0.14)	1.16 (0.16)	1.30 (0.33)	1.40 (0.49)	8.00 <sup>a</sup>	3/142	< <b>0.001</b>	0.14 <sup>e</sup>
CCI (range)	1.00–1.60	1.00–1.64	1.00–2.31	1.00–3.36				
TCDS	61.67 (7.84)	65.14 (9.05)	73.15 (18.81)	79.09 (27.74)	8.19 <sup>a</sup>	3/142	< <b>0.001</b>	0.15 <sup>e</sup>

CCI, Colour confusion index; TCDS, total colour distance score; MDMA, commonly known as ‘ecstasy’; df/df<sub>err.</sub>, degrees of freedom/degrees of freedom for errors; MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest; CCQ, Cocaine Craving Questionnaire.

<sup>a</sup> ANOVA (over all groups).

<sup>b</sup> Fisher’s exact test (over all groups).

<sup>c</sup>  $\chi^2$ -test for frequency data.

<sup>d</sup> Independent *t* test (cocaine users only).

<sup>e</sup>  $\eta^2$ .

<sup>f</sup> Cramer’s *V*, type I = red–green; type II = red–green and blue–yellow; type III = blue–yellow; type IV = no clear pattern.

Values are means and s.d. in parentheses, number of subjects and percentage.

Significant *p* values (*p* < 0.05) are shown in bold.

**Table 2.** Drug use parameters

	Stimulant-naïve controls ( <i>n</i> = 47)	Occasional MDMA users ( <i>n</i> = 23)	Occasional cocaine users ( <i>n</i> = 47)	Dependent cocaine users ( <i>n</i> = 29)
Nicotine				
Cigarettes/wk	59.33 (65.30)	74.83 (58.46)	83.18 (60.63)	122.64 (97.85)
Years of use	5.78 (7.39)	4.63 (3.23)	7.93 (6.11)	17.81 (11.16)
Alcohol				
g/wk	115.68 (137.18)	94.18 (106.74)	173.81 (154.12)	281.98 (382.02)
Cocaine				
g/wk	–	0.18 (0.55)	1.01 (1.08)	5.46 (6.77)
Years of use	–	0.52 (1.09)	4.58 (3.70)	12.32 (7.39)
Cumulative dose (g)	–	17.95 (47.50)	330.75 (470.01)	6495.38 (9148.92)
Last use (d)	–	34.00 (17.72) <i>n</i> = 5	26.29 (34.33)	18.95 (34.58)
Amphetamine				
g/wk	–	0.77 (1.27)	0.07 (0.24)	0.00 (0.01)
Years of use	–	2.71 (2.02)	1.20 (2.66)	1.28 (4.18)
Cumulative dose (g)	–	204.41 (264.83)	43.73 (127.13)	15.75 (61.85)
Last use (d)	–	86.33 (180.70) <i>n</i> = 18	172.61 (242.65) <i>n</i> = 20	81.63 (81.42) <i>n</i> = 4
MDMA				
Pills/wk	–	1.65 (2.69)	0.03 (0.12)	0.05 (0.12)
Years of use	–	2.79 (2.01)	1.38 (3.49)	2.57 (5.15)
Cumulative dose (pills)	–	442.36 (469.72)	37.88 (116.45)	235.42 (751.43)
Last use (d)	–	60.95 (157.25)	227.20 (280.00) <i>n</i> = 14	72.48 (52.01) <i>n</i> = 8
Cannabis				
g/wk	0.31 (0.73)	3.79 (4.55)	2.62 (5.95)	2.25 (5.66)
Years of use	3.15 (5.03)	3.76 (3.11)	6.19 (5.59)	9.63 (11.45)
Cumulative dose (g)	791.80 (4001.99)	1015.24 (1307.18)	1601.37 (3680.61)	4260.99 (8694.76)
Last use (d)	29.70 (44.94) <i>n</i> = 20	15.60 (26.69) <i>n</i> = 15	17.62 (28.99) <i>n</i> = 35	19.87 (25.12) <i>n</i> = 16
Hallucinogens				
Cumulative dose (times)	4.75 (3.37) <i>n</i> = 8	27.25 (40.97) <i>n</i> = 16	29.83 (65.48) <i>n</i> = 23	16.10 (23.14) <i>n</i> = 15
Last use (months)	38.50 (43.25) <i>n</i> = 8	6.31 (7.29) <i>n</i> = 16	40.07 (47.23) <i>n</i> = 23	112.60 (135.42) <i>n</i> = 15

MDMA, Commonly known as 'ecstasy'.

Use per week, duration of use and cumulative dose are averaged within the total group. Last use is averaged only for subjects who used the drug. In this case, sample size is shown.

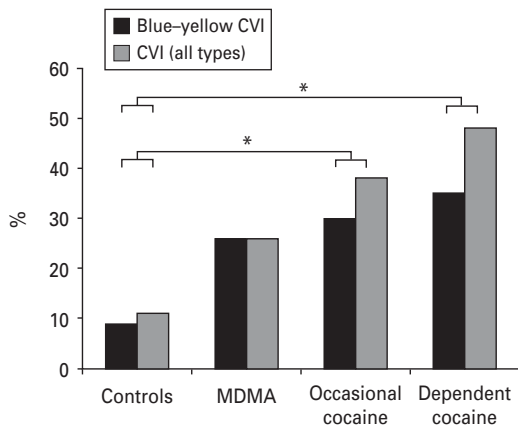
Values are means (s.d.).

was calculated. Neither the factor cannabis use nor the group  $\times$  cannabis use interaction was significant ( $F < 1.0$ ), whereas the group effect remained unchanged ( $F_{3,133} = 2.94$ ,  $p < 0.05$ ,  $\eta^2 = 0.06$ ). Given that 19 cocaine users were tested positive for cocaine in urine screening, we investigated the effect of acute cocaine effects on the CCI within cocaine users. In an ANCOVA (covariates see above) with group (occasional/dependent users) and urine test (positive/negative) as fixed-factors, both main effects were not significant ( $F < 0.20$ ). However, a disordinal group  $\times$  urine test interaction was found ( $F_{1,67} = 4.12$ ,  $p < 0.05$ ,  $\eta^2 = 0.06$ ), indicating that positive tested occasional cocaine users exhibited more pronounced CVI than negative tested occasional users, whereas positive

tested dependent users displayed less CVI than negative tested dependent users (Fig. 2).

#### *Sensitivity and specificity of the LD-15*

Sensitivity calculations indicated that the LD-15 correctly identified CVI (all types) in cocaine users in 42% of the cases. Specificity was 84%, indicating a false-positive rate of 16% for the controls and MDMA users. The positive predictive value (PPV) or, in other words, the probability that an individual actually exhibits CVI when a positive test result was observed was 74%. The negative predictive value (NPV) or the probability that an individual without CVI really is free from the condition was 57%. Sensitivity for



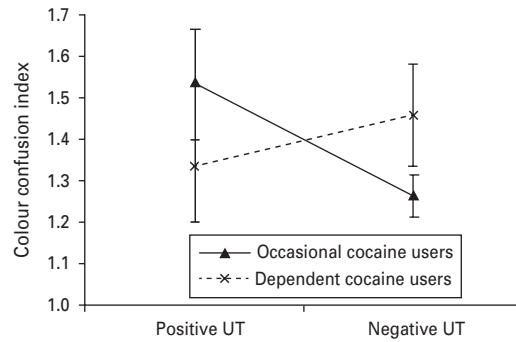
**Fig. 1.** Frequency of blue–yellow colour vision impairment (CVI) and all types of CVI (%) for stimulant-naïve controls, occasional MDMA (commonly known as ‘ecstasy’) users, occasional cocaine users and dependent cocaine users. \*\*  $\chi^2$ -test:  $p < 0.01$ ; \*\*\*  $\chi^2$ -test:  $p < 0.001$ .

blue–yellow CVI was 32%, specificity 91%, PPV 71% and NPV 54%.

#### Verbal learning and declarative memory performance

To investigate the association of CVI and memory performance, cocaine users with diagnosed CVI ( $Coc_{CVI}$ ), cocaine users without CVI ( $Coc_{non-CVI}$ ) and controls without CVI were compared (Table 3). ANCOVA analyses were corrected for age and years of education. Importantly,  $Coc_{CVI}$  and  $Coc_{non-CVI}$  did not significantly differ regarding cocaine use parameters. In general, cocaine users showed worse performance in the working memory span, recall after interference and delayed recall, when compared to controls. Moreover,  $Coc_{CVI}$  showed inferior performance compared to  $Coc_{non-CVI}$  in the supraspan, learning, recall consistency, delayed recall and recognition of lists A and B. Controls differed from  $Coc_{CVI}$  in all memory parameters.

In a second step, we investigated whether RAVLT performance scores were correlated with CCI scores and cocaine use (Table 4). Control subjects were excluded from this analysis in order to prevent inflation of existing associations and MDMA users because previous findings have shown that MDMA users exhibit marked verbal declarative memory deficits (Quednow *et al.* 2006). After controlling for age, the CCI correlated negatively with the supraspan, learning performance, delayed recall, adjusted recognition for list A, and positively with loss after consolidation, reflecting that more pronounced CVI was associated with worse memory performance. When



**Fig. 2.** Significant interaction between cocaine group (47 occasional *vs.* 29 dependent users) and urine toxicology (UT; 19 positive *vs.* 57 negative tests) ( $F_{1,67} = 4.12$ ,  $p < 0.05$ ). Means and S.E.M. are shown.

corrected for age, cocaine use, particularly lifetime use, was correlated with several memory parameters (Table 4), indicating worse memory performance with increasing cocaine use. Last cocaine use (d) was not significantly related to any of the RAVLT variables (data not shown).

#### Association between CVI, substance use and demographic data

In the total sample, CCI scores were correlated with age ( $r = 0.21$ ,  $p < 0.05$ ), years of education ( $r = -0.19$ ,  $p < 0.05$ ), cigarettes smoked per week ( $r = 0.17$ ,  $p < 0.05$ ) and years of smoking ( $r = 0.22$ ,  $p < 0.01$ ), indicating worse colour discrimination with increasing age, lower education and higher nicotine use. Alcohol and cannabis use, sex and verbal IQ were not associated with the CCI.

For the correlations between illegal drug use and the CCI (except for cannabis), control subjects were excluded to prevent inflating existing correlations. Alcohol, cannabis, amphetamine and MDMA use were not associated with the CCI. Only cocaine use (yr:  $r = 0.25$ ,  $p < 0.05$ ,  $n = 99$ ) and cocaine lifetime use (g;  $r = 0.25$ ,  $p < 0.05$ ,  $n = 99$ ) were positively correlated with the CCI. The effects remained after adjusting for age (both  $r = 0.20$ ,  $p < 0.05$ ). A binary logistic regression analysis (stepwise forward) examining the association of age, verbal IQ, years of education, cigarettes per week, alcohol use (g/wk), lifetime use of cannabis, amphetamine, cocaine (g) and MDMA (pills), with CVI indicated that the presence of dyschromatopsia was only related to cocaine lifetime use ( $\beta = 0.36$ ,  $p < 0.05$ ), whereas no significant associations were found with any other variables.

Cocaine craving (CCQ) was not significantly correlated with the CCI. Furthermore,  $Coc_{CVI}$  and



**Table 3.** Verbal learning/memory performance of controls without CVI and cocaine users with and without CVI

RAVLT parameters	Con ( $n=42$ )	Cocaine users without CVI ( $n=44$ )	Cocaine users with CVI ( $n=32$ )	$F$	$df/df_{err}$	$p$	<i>Sidak post-hoc group comparisons (<math>p &lt; 0.05</math>)</i>
Working memory span (trial 1)	9.58 (1.95)	8.67 (1.86)	8.13 (1.91)	4.91	2/113	<0.01	Con > Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>
Learning performance (trials $\Sigma 1-5$ )	63.42 (7.45)	60.21 (7.08)	55.38 (7.27)	10.12	2/113	<0.001	Con, Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>
Recall consistency, trials 1–5 (in percent)	92.67 (9.75)	90.04 (9.27)	84.71 (9.51)	5.95	2/113	<0.01	Con, Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>
Interference trial (list B)	8.97 (2.42)	8.29 (2.30)	7.36 (2.36)	3.88	2/113	<0.01	Con > Coc <sub>CVI</sub>
Recall after interference (trial 6)	13.44 (2.37)	12.14 (2.26)	11.25 (2.31)	7.54	2/113	<0.01	Con > Coc <sub>non-CVI</sub> , Coc <sub>CVI</sub>
Delayed recall (trial 7 after 30 min)	13.55 (2.11)	12.53 (2.00)	11.27 (2.06)	10.03	2/113	<0.001	Con > Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>
Loss after consolidation (trial 5 minus 7)	0.65 (1.47)	1.13 (1.40)	1.65 (1.44)	3.98	2/113	<0.01	Con > Coc <sub>CVI</sub>
Adjusted recognition list A [p(A) list A]	0.90 (0.11)	0.87 (0.11)	0.82 (0.11)	4.98	2/113	<0.01	Con, Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>
Adjusted recognition list B [p(A) list B]	0.82 (0.13)	0.77 (0.12)	0.70 (0.12)	6.73	2/113	<0.01	Con, Coc <sub>non-CVI</sub> > Coc <sub>CVI</sub>

CVI, Colour vision impairment; RAVLT, Rey Auditory Verbal Learning Test; Con, stimulant naive controls without CVI;  $df/df_{err}$ ; Coc<sub>CVI</sub>, cocaine users with CVI; Coc<sub>non-CVI</sub>, cocaine users without CVI.

Values are means adjusted for age and years of education (s.d.).

**Table 4.** Correlations between memory performance, CCI and cocaine use parameters in cocaine users

	CCI	Cocaine (g/wk)	Cocaine (years of use)	Cocaine (lifetime in g)	Cocaine (max. in g/d)
Supraspan	<b>−0.27 (0.02)</b>	−0.22 (0.06)		<b>−0.36 (0.001)</b>	<b>−0.39 (0.004)</b>
Learning performance (trials $\Sigma 1-5$ )	<b>−0.33 (0.004)</b>	<b>−0.26 (0.02)</b>	<b>−0.25 (0.03)</b>	<b>−0.38 (0.001)</b>	<b>−0.33 (0.006)</b>
Recall consistency, trials 1–5 (in %)		−0.20 (0.09)	−0.23 (0.06)	<b>−0.30 (0.01)</b>	−0.22 (0.06)
Interference trial (list B)	−0.19 (0.10)			−0.21 (0.07)	−0.20 (0.09)
Recall after interference (trial 6)	−0.19 (0.10)	<b>−0.34 (0.003)</b>	<b>−0.29 (0.01)</b>	<b>−0.33 (0.004)</b>	<b>−0.27 (0.03)</b>
Delayed recall (trial 7 after 30 min)	<b>−0.27 (0.02)</b>	−0.21 (0.07)	−0.20 (0.09)	<b>−0.31 (0.008)</b>	
Loss after consolidation (trial 5 minus 7)	<b>0.24 (0.04)</b>				
Adjusted recognition list A [p(A) list A]	<b>−0.26 (0.02)</b>		<b>−0.30 (0.008)</b>	<b>−0.33 (0.004)</b>	<b>−0.28 (0.02)</b>
Adjusted recognition list B [p(A) list B]	−0.22 (0.06)	−0.22 (0.06)	−0.22 (0.06)	<b>−0.39 (0.001)</b>	<b>−0.36 (0.002)</b>

CCI, Colour confusion index.

Correlations are adjusted for age. Correlations with a  $p$  level < 10% are shown, while significant correlations ( $p < 0.05$ ) are shown in bold.

Partial correlation  $r$  with  $p$  values shown in parentheses.

Coc<sub>non-CVI</sub> did not significantly differ in their CCQ scores (data not shown).

## Discussion

Occasional and dependent cocaine users both showed more frequent and more intense CVI, predominantly

in the blue–yellow spectrum, in comparison to psychostimulant-naïve controls. CVI in dependent cocaine users was more pronounced than in occasional cocaine users, as indicated by the larger effect sizes and the higher prevalence of CVI in the qualitative data. However, it is noteworthy that CVI was already highly frequent in occasional cocaine users. MDMA

users with low exposure to dopaminergic stimulants did not show changes in colour vision but MDMA users who had often used amphetamine showed similar blue–yellow CVI as cocaine users. Higher CCI was related to higher cumulative lifetime cocaine use and longer duration of use. Moreover, the presence of CVI was clearly associated with diminished verbal declarative memory performance in cocaine users, possibly reflecting a potential relationship between retinal and cerebral dopaminergic alterations. Overall, these results support the notion that CVI, particularly blue–yellow CVI, is specific for drugs mainly altering the dopamine system, such as cocaine and amphetamine.

The present findings are largely consistent with previous studies providing evidence that blue–yellow CVI prevails in withdrawn cocaine-dependent patients (Desai *et al.* 1997; Roy *et al.* 1996, 1997a, b, 2003). However, our report elaborated on this finding by showing that occasional cocaine and amphetamine use was associated with blue–yellow CVI and that a different pattern applies for occasional stimulant use regarding abstinence. The authors of prior studies proposed that the CVI was due to the effect of cocaine on dopaminergic retinal neurotransmission leading to a hypodopaminergic state and not owing to the effect of cocaine on ocular blood vessels, as a careful examination indicated no retinal lesions. Compared to Desai *et al.* (1997), who reported that 48% of the dependent cocaine users exhibited blue–yellow CVI, a lower prevalence of 35% for dependent and 30% for occasional cocaine users was found in the present sample. However, this may be due to slightly different error classifications between both studies, as we found that 48% of the dependent and 38% of the occasional cocaine users showed CVI when all types of CVI were considered. Furthermore, in our study, 19 of 76 users tested positive for cocaine in urine toxicology and may not have been suffering from an acute hypodopaminergic state. In accordance with Desai *et al.* (1997), no significant correlation between CVI and days of cocaine abstinence was found in the present results. Moreover, Roy *et al.* (1996, 1997a) found that cocaine-dependent patients with an ERG blue cone b-wave amplitude  $<0.5$  mV reported stronger cocaine craving, which is in line with the finding that reduced  $D_2$  receptor binding in the dorsal striatum during a cocaine-cue condition was linked to self-reports of cocaine craving (Volkow *et al.* 2006). In contrast, cocaine users with CVI in the present sample did not report stronger cocaine craving than cocaine users without CVI. Given that Roy *et al.* (1996, 1997a, b) had used the 45-item version of the CCQ, differences in the magnitude of the reported craving scores cannot be

directly compared. Nevertheless, cocaine users from the present study may have experienced less craving, as several users had tested positive for cocaine in the urine analysis.

Earlier studies have not examined the relationship between CVI and drug use patterns in detail. In the present report, CVI was correlated with lifetime quantity and duration of cocaine use, supporting the view that CVI might be cocaine-induced. However, the cross-sectional design of the study does not allow a final conclusion regarding causality. Even though dependent cocaine users were more strongly impaired in colour vision discrimination than occasional cocaine users, the relatively small difference between the two groups raises the question as to whether a hypodopaminergic state could be a pre-morbid trait that functions as a risk factor or possibly that CVI may be due to a predisposition  $\times$  substance-induced effects interaction. Although abstinence period since last cocaine use was not directly related to LD-15 performance, it is noteworthy that occasional cocaine users showed better colour discrimination when the urine toxicology tested negative for recent cocaine use, while dependent cocaine users performed better when they were tested positive. A potential explanation could be that the hypodopaminergic state was less severe in occasional cocaine users; therefore, acute dopamine release had no beneficial effect on their colour discrimination ability. Furthermore, neither alcohol nor any of the other psychoactive drugs were significantly related to CVI in cocaine users. Finally, it was not possible to identify a threshold value as to after which cocaine doses CVI occurs. However, for both occasional and dependent cocaine users, duration and quantity of cocaine use were most strongly related to CVI.

MDMA users who had co-used amphetamine showed blue–yellow CVI, while MDMA users who had used little amphetamine did not exhibit blue–yellow CVI. The correlation between CVI and amphetamine use was not significant, but only a few subjects reported amphetamine use and thus the power to detect a dose–response relationships was low. Although some animal studies have yielded evidence that MDMA, at least acutely and in a much less potent manner than amphetamine-like derivatives (Partilla *et al.* 2006), also increases synaptic dopamine levels and dopamine efflux (Baumann *et al.* 2007; Yamamoto & Bankson, 2005), the majority of the studies only reported selective neurotoxicity for 5-HT-containing neurons (for review, see Capela *et al.* 2009). It is currently controversial if cocaine use can also be neurotoxic for dopaminergic neurons; however, recent

human post-mortem studies support this notion (Little *et al.* 2009; Okvist *et al.* 2011).

We have demonstrated that CVI was associated with working memory span, encoding and retrieval deficits in cocaine users. In line with the present results, several measures of verbal memory, attentional performance and executive function have consistently revealed deficits in withdrawn cocaine users (Fernandez-Serrano *et al.* 2009; Goldstein *et al.* 2004; Kelley *et al.* 2005; Woicik *et al.* 2009). Many cognitive processes, working memory and executive functions, in particular, are mediated by the PFC, which is strongly dependent on intact dopamine signalling (Braskie *et al.* 2008; Nieoullon, 2002; Vernaleken *et al.* 2007). Accordingly, cocaine users with CVI displayed worse performance in memory parameters previously associated with the PFC, such as working memory span and recall consistency (Quednow *et al.* 2006). Given that cocaine use may exert its influence on both cognition and colour vision, a possible link between alterations in the frontostriatal and retinal dopamine system is self-evident. Prior studies have indeed provided evidence pointing in this direction. As mentioned above, decreased blue cone b-wave ERG amplitudes in dependent cocaine users were associated with lower concentrations of CSF HVA (Roy *et al.* 2003), and reduced striatal D<sub>2</sub> receptor availability was related to lower metabolic activity in the medial PFC and the anterior cingulate gyrus persisting 3–5 months after detoxification (Volkow & Li, 2004; Volkow *et al.* 1988, 1991, 1993). However, the specific mechanism of how dopamine mediates colour vision discrimination remains elusive and it is unclear how stimulant use precisely affects retinal dopamine transmission. Naturally, the question arises as to what extent alterations in the frontostriatal and retinal dopamine system may be linked. Combining cerebral molecular imaging with ophthalmological/electrophysiological methods could greatly contribute to a better understanding of the exact mechanism by which blue–yellow CVI and cognitive dysfunction occur. In some studies, it was postulated that short wavelength-sensitive cones (blue cones) may generally be more vulnerable to toxic noxa and ageing than medium and long wavelength-sensitive cones, possibly due to their relative scarcity and anatomical distribution (Djamgoz *et al.* 1997; Hart, 1987; Masson *et al.* 1993; Witkovsky, 2004). Moreover, mammalian studies report that certain cell types in the retina have selective blue-cone input that is mediated by dopamine transmission (Djamgoz *et al.* 1997).

Eventually, the usefulness of the LD-15 as a marker for dopaminergic and cognitive alterations shall be

addressed. The present results imply that although the specificity of the LD-15 was good, its sensitivity is not high enough for diagnostic and predictive purposes regarding blue–yellow CVI in cocaine users. Roy *et al.* (1997a, b, 2003) have previously suggested that ERG blue cone b-wave amplitudes may serve as a neurobiological marker related to central dopamine function in cocaine-dependent patients. It would be of interest to further investigate the correspondence between ERG blue cone amplitudes and the LD-15 and cognitive deficits.

Some limitations inherent to the investigation of CVI were present in this study. Colour vision is influenced by several factors besides stimulant use, such as age, alcohol and nicotine use. However, occasional cocaine users, MDMA users and controls were well matched and potentially confounding variables were controlled in the analyses. The sensitivity of the LD-15 is limited and blue–yellow CVI also occurred in controls, although to a much lower extent. Furthermore, the possibility that some cocaine users may have suffered minor ocular blood vessel bursts cannot be ruled out since participants did not undergo an ophthalmological examination. Nevertheless, results from prior studies controlling for blood vessel damage are consistent with the findings of the current study (Desai *et al.* 1997; Roy *et al.* 1996). Moreover, in addition to alterations in dopaminergic transmission in the retina, sub-cortical and cortical processing may also be affected and contribute to decreased colour discrimination ability (Conway *et al.* 2010). Finally, the history of drug consumption was assessed only by means of self-reports, precluding the calculation of lifetime drug use objectively (Curran, 2000).

## Conclusion

In conclusion, this study provided evidence that drug users consuming stimulants that mainly alter the dopaminergic neurotransmitter system exhibit more frequent blue–yellow CVI and that stimulant users with an occasional cocaine use pattern are affected to a similar extent as chronic users. Furthermore, CVI was found to be associated with decreased performance in verbal learning and memory in occasional and dependent cocaine users, implying that retinal and cerebral dopaminergic alterations could be linked to a certain degree.

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## Conflict of Interest

None.

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